



Atraumatic (pencil-point) versus conventional needles for lumbar puncture a clinical practice guideline

Rochwerg, Bram; Almenawer, Saleh A; Siemieniuk, Reed A C; Vandvik, Per Olav; Agoritsas, Thomas; Lytvyn, Lyubov; Alhazzani, Waleed; Archambault, Patrick; D'Aragon, Frederick; Farhoumand, Pauline Darbellay; Guyatt, Gordon; Laake, Jon Henrik; Beltrán-Arroyave, Claudia; McCredie, Victoria; Price, Amy; Chabot, Christian; Zervakis, Tracy; Badhiwala, Jetan; St-Onge, Maude; Szczeklik, Wojciech; Møller, Morten Hylander; Lamontagne, Francois

Published in:
BMJ (Clinical research ed.)

DOI:
[10.1136/bmj.k1920](https://doi.org/10.1136/bmj.k1920)

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

Document license:
[CC BY-NC](#)

Citation for published version (APA):
Rochwerg, B., Almenawer, S. A., Siemieniuk, R. A. C., Vandvik, P. O., Agoritsas, T., Lytvyn, L., Alhazzani, W., Archambault, P., D'Aragon, F., Farhoumand, P. D., Guyatt, G., Laake, J. H., Beltrán-Arroyave, C., McCredie, V., Price, A., Chabot, C., Zervakis, T., Badhiwala, J., St-Onge, M., ... Lamontagne, F. (2018). Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline. *BMJ (Clinical research ed.)*, 361, 1-6. [k1920]. <https://doi.org/10.1136/bmj.k1920>

Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline

Bram Rochwerf,^{1 2} Saleh A Almenawer,³ Reed A C Siemieniuk,^{2 4} Per Olav Vandvik,^{5 6} Thomas Agoritsas,^{2 7} Lyubov Lytvyn,² Waleed Alhazzani,^{1 2} Patrick Archambault,^{8 9 10} Frederick D'Aragon,^{11 12} Pauline Darbellay Farhoumand,⁷ Gordon Guyatt,² Jon Henrik Laake,¹³ Claudia Beltrán-Arroyave,¹⁴ Victoria McCredie,^{4 15} Amy Price,^{16 17} Christian Chabot,¹⁸ Tracy Zervakis,¹⁹ Jetan Badhiwala,²⁰ Maude St-Onge,^{10 21 22} Wojciech Szczeklik,²³ Morten Hylander Møller,^{24 25} Francois Lamontagne^{11 12}

Full author details can be found at the end of the article
Correspondence to: F Lamontagne
francois.lamontagne@usherbrooke.ca

Cite this as: *BMJ* 2018;361:k1920
doi: 10.1136/bmj.k1920

This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicproject.org) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

Is the needle tip configuration important when performing a lumbar puncture for any indication? A systematic review published in the *Lancet* in December 2017 suggests that it is. The review found that using atraumatic (pencil-point) lumbar puncture needles instead of conventional lumbar puncture needles reduced the risk of post-dural-puncture headache and of return to hospital for additional pain control.¹ This guideline recommendation aims to promptly and transparently translate this evidence to a clinical recommendation, following standards for GRADE methodology and trustworthy guidelines.² The *BMJ* Rapid Recommendations panel makes a strong recommendation for the use of atraumatic needles for lumbar puncture in all patients regardless of age (adults and children) or indication instead of conventional needles.^{3 4} Box 1 shows the article and evidence linked to this Rapid Recommendation. The main infographic provides an overview of the absolute benefits and harms (although none were present here) of atraumatic needles. Table 1 below shows any evidence that has emerged since the publication of this guideline.

Box 1 | Linked resources for this *BMJ* Rapid Recommendations cluster

- Rochwerf B, Almenawer SA, Siemieniuk RAC, et al. Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline. *BMJ* 2018;361:k1920
– Summary of the results from the Rapid Recommendation process
- Nath S, Koziazar A, Badhiwala JH, et al. Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. *Lancet* 2018;391:1197-204
– Review of all available randomised trials comparing the use of atraumatic needles and conventional needles for any lumbar puncture indication
- MAGICapp (www.magicapp.org/public/guideline/j7A5Gn)
– Expanded version of the results from the Rapid Recommendation process with multilayered recommendations, evidence summaries, and decision aids for use on all devices

WHAT YOU NEED TO KNOW

- Post-dural-puncture headache is a common complication after lumbar puncture, affecting up to 35% of patients
- This headache results from sustained leakage of cerebrospinal fluid from a dural tear; it can be debilitating and require return to hospital for narcotics or invasive therapy
- We issue a strong recommendation for use of atraumatic needles in all patients (adults and children) undergoing lumbar puncture because they decrease complications and are no less likely to work than conventional needles
- Atraumatic needles are more expensive, but evidence suggests that they reduce costs overall compared with conventional needles

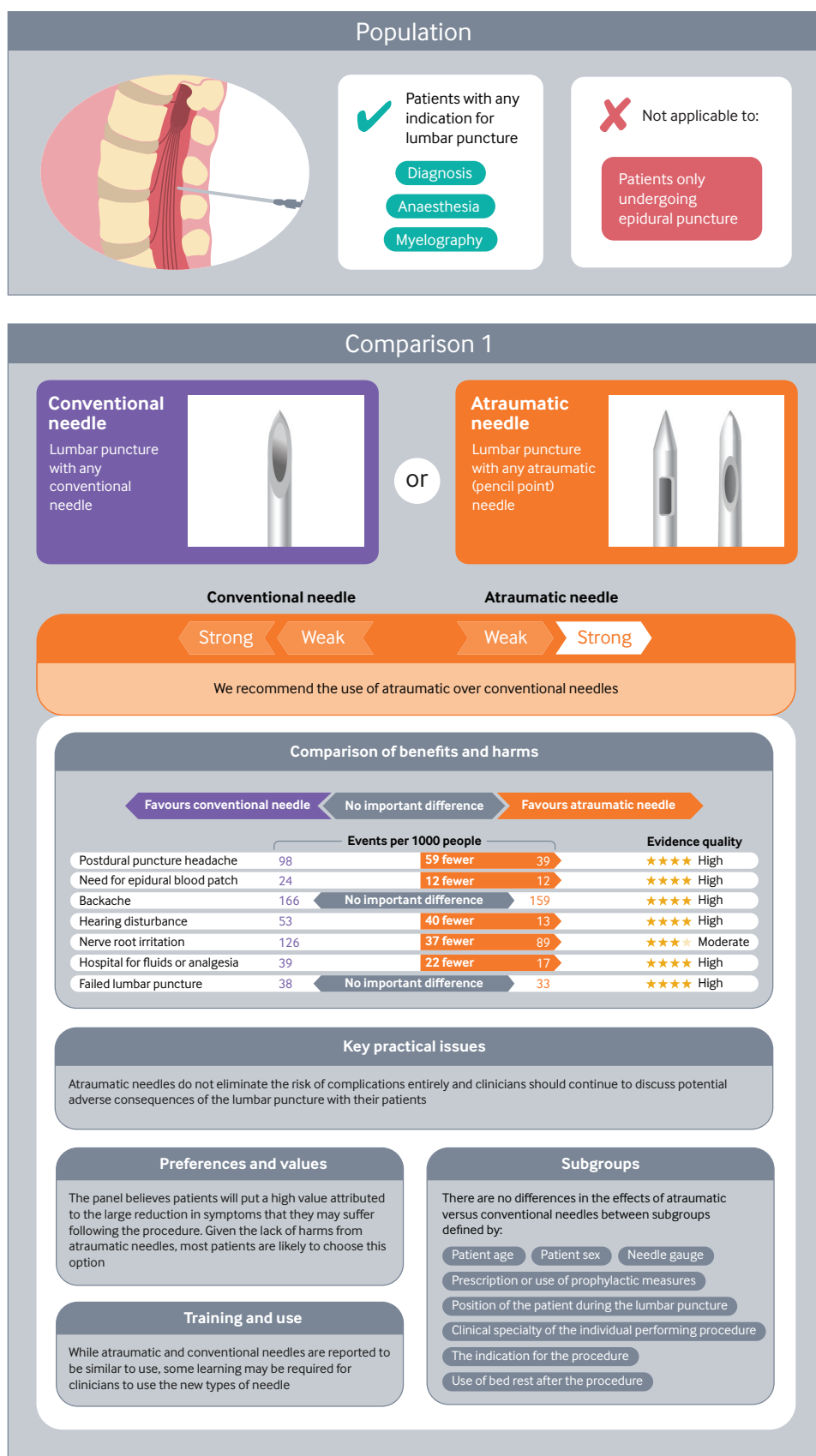
Current practice

Physicians perform lumbar punctures for diagnostic or therapeutic purposes. Among the complications associated with this procedure, post-dural-puncture headache is the most common, affecting up to 35% of patients.⁵ This complication can be debilitating, requiring return visits to the hospital for controlled analgesia, invasive therapy, or increased hospital duration of stay.^{5 6}

Post-dural-puncture headache, among other adverse effects of lumbar punctures, is attributed to the leakage of cerebrospinal fluid from the dural defect into the epidural space that is created by the spinal needle during puncture.

Conventional needles have a sharp tip (designed to cut through tissues) and a distal opening. In comparison, atraumatic needles are more blunt with a closed pencil-point or cone shaped tip and a side port for injection or collection.¹

Cadaveric studies using histological examination have shown that, compared with conventional needles, atraumatic needles more often separate and dilate surrounding dural fibres rather than cutting through them. Subsequent contracture of the fibres after needle removal results in a small pinpoint opening in the dura, as opposed to the



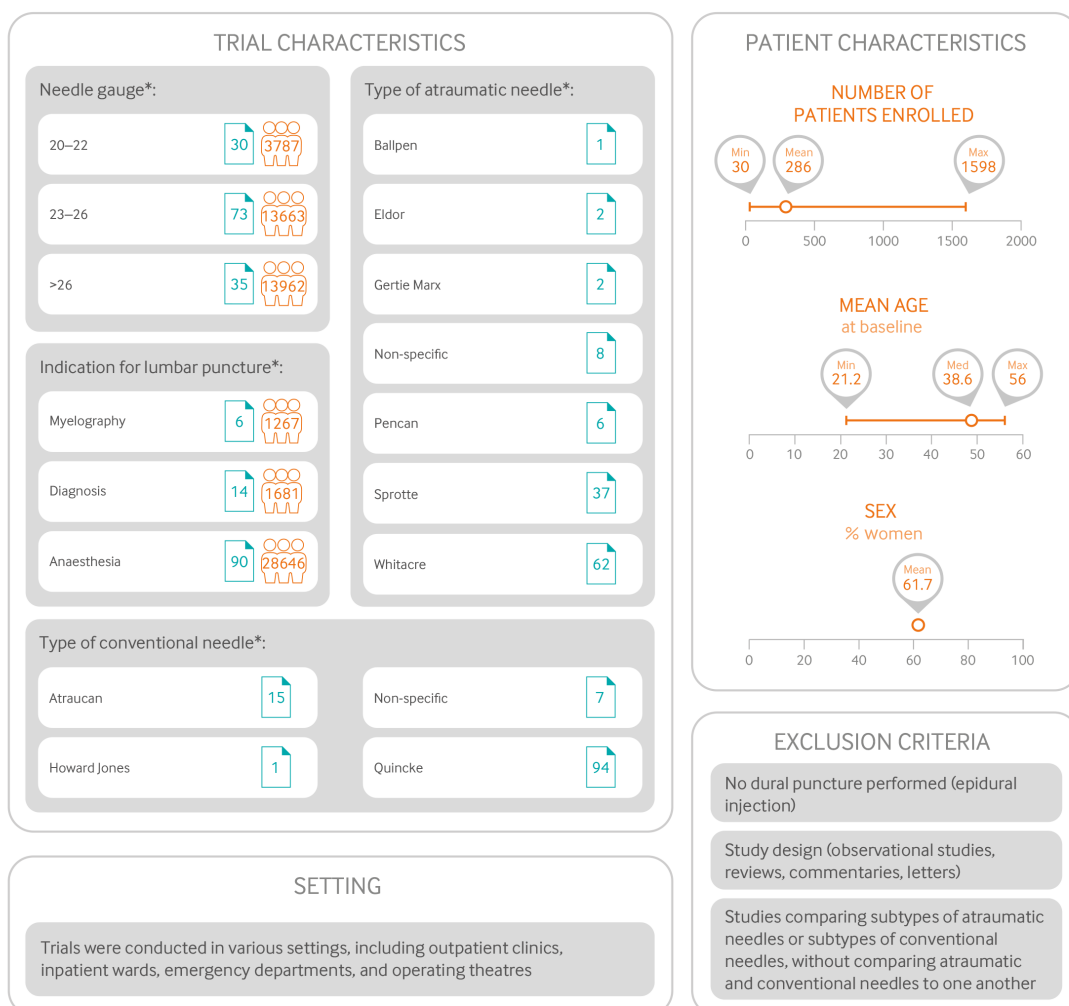
Disclaimer: This infographic is not a clinical decision aid. This information is provided without any representations, conditions or warranties that it is accurate or up to date. BMJ and its licensors assume no responsibility for any aspect of treatment administered with the aid of this information. Any reliance placed on this information is strictly at the user's own risk. For the full disclaimer wording see BMJ's terms and conditions: <http://www.bmj.com/company/legal-information/>

DATA SOURCES

Use this information to gauge how similar your patients' conditions are to those of people studied in the trials

NUMBER OF TRIALS 110

NUMBER OF PATIENTS 31 412



*Note number of trials do not add to 110 trial and percentages do not add to 100% as some trials examined more than one needle type, subtype, gauge, and indication.

Graphic 2 | Characteristics of patients and trials included in systematic review of the effects of needle type on the risk of major adverse effects associated with lumbar puncture

irregular and larger opening created by conventional needles.⁷ Use of atraumatic needles may therefore reduce the incidence of post-dural-puncture headache by limiting the leakage of cerebrospinal fluid after lumbar puncture. Surveys indicate that use of atraumatic needles in routine clinical practice is limited.^{8–10}

Although terminology varies, for the purposes of this guideline, we will refer to atraumatic needles and conventional needles, which have a sharp tip to cut through tissues with a distal tip opening.

The evidence

The systematic review summarised the results of 110 randomised clinical trials (RCTs) conducted between 1989 and 2017 in 29 countries (including both high and

middle/low income): it suggests that atraumatic needles consistently reduce the risk of major adverse effects associated with lumbar puncture done for any indication compared with conventional needles. More specifically, the risk of post-dural-puncture headache was significantly reduced when atraumatic needles were used for lumbar puncture (relative risk 0.40 (95% confidence interval 0.34 to 0.47)). Graphic 2 presents an overview of the number and types of patients, as well as a summary of the benefits and harms (although none were present here) of atraumatic needles for lumbar punctures.

Individuals who were included in the eligible studies underwent lumbar punctures for any diagnostic or therapeutic indication. Baseline characteristics were similar between atraumatic and conventional needle groups,

HOW THIS RECOMMENDATION WAS CREATED

The recent publication of a systematic review and meta-analysis of studies comparing atraumatic with conventional needles for any lumbar puncture triggered the following guideline recommendation.¹ The Rapid Recommendations team believed that the results of this systematic review, which considered the full body of evidence, had important clinical implications and might change practice.²

Our international panel—including intensivists, neuro-intensivists, internists, anaesthesiologists, neurologists, neurosurgeons, emergency physicians, paediatricians, methodologists, and people with lived experience of lumbar puncture and caring for those with lumbar puncture—decided on the scope of the recommendation and the outcomes most important to patients (see appendix 1 on [bmj.com](#)). The panel met to discuss the evidence and formulate a recommendation. No panel member had financial conflicts of interest; intellectual and professional conflicts were minimised and transparently described (appendix 2 on [bmj.com](#)).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,^{2,11} including using the GRADE approach to critically appraise the evidence and create recommendations (see appendix 3 on [bmj.com](#)).³ The panel considered the benefits, as well as any harms, and burdens of atraumatic needles, the certainty (quality) of the evidence for each outcome, typical and expected variations in patient values and preferences, acceptability, feasibility, and resource implications.¹² Following the GRADE based approach, recommendations can be strong or weak (also known as conditional) for or against a specific course of action.¹³

The panel identified 13 patient-important outcomes to inform the recommendation: post-dural-puncture headache (severe or mild), any headache (including those not meeting the exact definition of post-dural-puncture), backache, hearing disturbance, nerve root irritation, traumatic tap, need to return to hospital for intravenous fluids or controlled analgesia or for an epidural blood patch, failed lumbar puncture, successful lumbar puncture on first attempt, and cerebrospinal fluid drainage efficiency. There was disagreement among panel members whether to include this last outcome (drainage efficiency), but it was specifically prioritised by one of the patients. At least one of the included studies reported on all of these outcomes except for drainage efficiency, although the number of participants included in the analysis for each outcome varied. A few other patient-important outcomes such as mortality, brain herniation, quality of life, and permanent paralysis were considered, but their incidence after lumbar puncture was considered to be too rare to be informative to the recommendation.

with the exception of needle gauge, which was larger in the conventional needle group (larger gauge equals smaller needle diameter).

Only 1065 of the 31 412 participants were children (3%). The proportion of elderly participants was unknown. The results were consistent across the predefined subgroups including:

- Age <18 v ≥18 years old
- Males v females,
- Bed rest after lumbar puncture v no bed rest
- Prophylactic intravenous fluids v no prophylactic intravenous fluids
- Needle gauge (small v large)
- Lateral v sitting position during lumbar puncture
- Indication for lumbar puncture (anaesthesia v diagnosis v myelography)
- Clinical specialty of person doing the lumbar puncture (radiologist v neurologist v anaesthesiologist).

Understanding the recommendation

The guideline panel makes a strong recommendation for the use of atraumatic over conventional needles in lumbar puncture for any indication because the benefits are perceived to be large with no associated harm.

The panel is confident that the recommendation applies to all patients (adults and children) who require a lumbar puncture and all physicians as the results were consistent across all predefined subgroups mentioned above.

In addition the panel agreed that there is minimal variability in patient preferences to favour the use of atraumatic needles.¹

Absolute benefits and harms

The main infographic explains the recommendation and provides an overview (GRADE summary of findings) of the absolute benefits of atraumatic needles. Estimates of baseline risk for effects are generated from the control arms of the included trials.¹ The infographic also leads to point-of-care formats in the MAGICapp.¹⁴

The panel was confident that:

- Use of atraumatic needles meaningfully decreases the risk of postdural puncture headache (both severe and mild), any headache, hearing disturbance, nerve root irritation, return to hospital for intravenous fluids and controlled analgesia or need for epidural blood patch (GRADE high to moderate quality evidence)
- Use of atraumatic needles has little or no effect on the risk of backache (GRADE high quality evidence)
- Use of atraumatic needles has little or no effect on the incidence of traumatic tap, failed lumbar puncture, and probability of success on first attempt (GRADE high to moderate quality evidence)
- There are no differences in the effects of atraumatic versus conventional needles between subgroups defined by age and sex of patients, the prescription or use of prophylactic measures, needle gauge, position of the patient during the lumbar puncture, the clinical specialty of the individual performing the lumbar puncture, or the indication for the procedure
- It is unlikely that new information will change interpretation for outcomes for which the evidence is of high to moderate quality.

The panel was less confident about whether:

- Use of atraumatic needles affects the efficiency of cerebrospinal fluid drainage (that is, the time required to draw the necessary amount of cerebrospinal fluid) regardless of the indication. It is likely there are other more important factors that influence drainage efficiency than just needle type. Also, this outcome is of varying importance depending on the context and indication for lumbar puncture.
- The panel believed that the recommendation is generalisable even to patients who are unconscious, such as those who are mechanically ventilated and sedated in the intensive care unit as data suggests that post-dural-puncture headache can persist for several days and can be felt even under sedation. Increased pain in this population may lead to undesirable indirect effects such as increased heart rate and increased sedation or analgesic requirement.

Values and preferences

The panel placed high value on the large reduction in symptoms. The panel believes that values and preferences regarding all important outcomes are unlikely to vary greatly across patients, particularly given the lack of detectable harm from atraumatic needles. We do not

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two people with lived experience of lumbar punctures, and one person with experience as a patient and a carer, were members of the guidance panel and authors. They identified and rated outcomes, and led the discussion on values and preferences. The patient partners rated all included outcomes as important to them. Although these values may not be shared by all patients for all outcomes considered, the panel expected little variation in how much importance other patients would place on the main outcomes of severe post-dural-puncture headache and the need to return to the hospital for an epidural blood patch. All panel members participated in the teleconferences and email discussions and met all authorship criteria.

anticipate that patients would opt for lumbar puncture needles associated with a greater risk of severe headaches. In contrast, the panel believes that there is considerable variability in how much importance individual patients and physicians attribute to traumatic taps (lumbar punctures contaminated with red blood cells negatively affecting fluid analysis). Accordingly, this outcome was considered to have limited importance in the recommendation.

The panel felt confident that atraumatic needles would be acceptable to patients, although this was not measured in the systematic review. Most clinicians found atraumatic and conventional needles similar to use. Some clinicians expressed potential concern regarding puncturing of the skin with the blunter atraumatic needle; however, this can be overcome by inserting the lumbar puncture needle through the same skin hole used for local anaesthesia, by using an introducer needle, or by spinning the atraumatic needle around its axis while advancing the needle.¹

Practical issues and other considerations

Atraumatic needles do not eliminate the risk of complications entirely, and clinicians should continue to discuss potential adverse consequences of the lumbar puncture with their patients.

Costs and resources

The panel reviewed three published cost-effectiveness studies.¹⁵⁻¹⁷ In those studies, the per-unit cost of atraumatic needles was greater than the cost of conventional needles, but atraumatic needles were ultimately cost-reducing because of the decreased need for additional care (perspective of the third-party payer) and lost working hours for patients (perspective of the patients and society). Moreover, as with conventional needles, the per-unit cost varies with the specific needle subtype and manufacturer.

Uncertainties

Addressing the following remaining knowledge gaps may inform decision makers and future guideline recommendations:

- Given the plausible greater risk of spinal stenosis and degenerative process in elderly patients who require a lumbar puncture, is the success rate for atraumatic and conventional needles similar in this population?

New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

EDUCATION INTO PRACTICE

- When performing a lumbar puncture, which needles do you use? Why?
- Based on this article how do you think your personal practice might change? Is there anything that you would say to a patient or do differently?
- How might you share this information with your organisation or review local policies on needle choice?
- Are certain subtypes of atraumatic needles (such as Cappe-Deutsch, Eldor, Gertie-Marx, Microtip, Sprotte, or Whitacre) associated with greater reduction in adverse events than others?

Updates to this article

The table shows evidence which has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 2 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions. Three authors of the systematic review were on the guideline panel (WA, SAA, JB).

Funding: This guideline was not funded.

Transparency: B Rochweg affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

- Nath S, Koziarz A, Badhiwala JH, et al. Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. *Lancet* 2018;391:1197-204. 10.1016/S0140-6736(17)32451-0 pmid:29223694.
- Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. 10.1136/bmj.i5191 pmid:27680768.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD pmid:18436948.
- Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; eds. Graham R, Mancher M, Miller Wolman D, et al. *Clinical practice guidelines we can trust*. National Academies Press, 2011. <https://www.ncbi.nlm.nih.gov/books/NBK209539/>.
- Lavi R, Yarnitsky D, Rowe JM, Weissman A, Segal D, Avivi I. Standard vs atraumatic Whitacre needle for diagnostic lumbar puncture: a randomized trial. *Neurology* 2006;67:1492-4. 10.1212/01.wnl.0000240054.40274.8a pmid:17060584.
- Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth* 2003;91:718-29. 10.1093/bja/aeg231 pmid:14570796.
- Celleno D, Capogna G, Costantino P, Catalano P. An anatomic study of the effects of dural puncture with different spinal needles. *Reg Anesth* 1993;18:218-21.pmid:8398954.
- Birnback DJ, Kuroda MM, Sternman D, Thys DM. Use of atraumatic spinal needles among neurologists in the United States. *Headache* 2001;41:385-90. 10.1046/j.1526-4610.2001.111006385.x pmid:11318885.
- Davis A, Dobson R, Kaninia S, Giovannoni G, Schmierer K. Atraumatic needles for lumbar puncture: why haven't neurologists changed? *Pract Neurol* 2016;16:18-22. 10.1136/practneurol-2014-001055 pmid:26349834.

- 10 Moisset X, Ruet A, Brochet B, et al. Who performs lumbar puncture, how many do they perform, how and why? A retrospective study of 6,594 cases. *Eur Neurol* 2016;76:8-11. 10.1159/000447452 pmid:27336667.
- 11 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. 10.1136/bmj.i5085 pmid:27680583.
- 12 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. 10.1016/j.jclinepi.2013.02.003 pmid:23570745.
- 13 Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008;336:1049-51. 10.1136/bmj.39493.646875.AE pmid:18467413.
- 14 Agoritsas T, Heen AF, Brandt L, et al. Decision aids that really promote shared decision making: the pace quickens. *BMJ* 2015;350:g7624. 10.1136/bmj.g7624 pmid:25670178.
- 15 Dakka Y, Warra N, Albadareen RJ, Jankowski M, Silver B. Headache rate and cost of care following lumbar puncture at a single tertiary care hospital. *Neurology* 2011;77:71-4. 10.1212/WNL.0b013e318220abc0 pmid:21593442.
- 16 Engedal TS, Ørding H, Vilholm OJ. Changing the needle for lumbar punctures: results from a prospective study. *Clin Neurol Neurosurg* 2015;130:74-9. 10.1016/j.clineuro.2014.12.020 pmid:25590665.
- 17 Tung CE, So YT, Lansberg MG. Cost comparison between the atraumatic and cutting lumbar puncture needles. *Neurology* 2012;78:109-13. 10.1212/WNL.0b013e31823efca9 pmid:22205758.

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

¹Department of Medicine, McMaster University, Hamilton, Ontario, Canada

²Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

³Division of Neurosurgery, McMaster University, Hamilton, Canada

⁴Department of Medicine, University of Toronto, Toronto, Ontario, Canada

⁵Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway

⁶Department of Medicine, Innlandet Hospital Trust-division, Gjøvik, Norway

⁷Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland

⁸Department of Family Medicine and Emergency Medicine & Department of Anesthesiology and Critical Care Medicine, Université Laval, Québec City, Canada

⁹Centre intégré de santé et de services sociaux de Chaudière-Appalaches, Centre hospitalier affilié universitaire Hôtel-Dieu de Lévis, Lévis, Canada

¹⁰CHU de Québec - Université Laval Research Center, CHU de Québec - Université Laval, Université Laval, Québec City, Canada

¹¹Faculty of Medicine and Health Sciences Université de Sherbrooke, Sherbrooke, Canada

¹²Research Centre, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada

¹³Department of Anaesthesiology, Division of Emergency and Critical Care, Rikshospitalet Medical Centre, Oslo University Hospital, Oslo, Norway

¹⁴Department of Pediatrics, Universidad de Antioquia, Medellín, Colombia

¹⁵Division of Critical Care Medicine, Department of Medicine, University Health Network, Toronto, Canada

¹⁶The BMJ (Research and Evaluation), London, UK

¹⁷Department of Continuing Education, University of Oxford, Oxford, UK

¹⁸McGill University, Montreal, Canada

¹⁹Virginia, USA

²⁰Department of Surgery, University of Toronto, Toronto, Canada

²¹Centre intégré de santé et de services sociaux de la Capitale-Nationale, Québec City, Canada

²²Department of Family and Emergency Medicine & Department of Anesthesiology and Critical Care & Faculty of Medicine, Université Laval, Laval, Canada

²³Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Kraków, Poland

²⁴Department of Intensive Care, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

²⁵Centre for Research in Intensive Care (CRIC), Copenhagen, Denmark